Remarks

I. Status of the Application and Claims

As originally filed, the present application had a total of 17 claims. Claims 1-4, 8, and 10-17 were withdrawn as the result of a restriction requirement. The remaining claims were cancelled during prosecution and new claims were added. The claims presently pending in the application are 18-26 and 30-40. All of these have been rejected under 35 U.S.C. § 101. In addition, claims 39 and 40 have been rejected under 35 U.S.C. § 112, second paragraph.

II. The Rejections

A. Rejection of Claims Under 35 U.S.C. § 101

On pages 2-4 of the Office Action, a rejection of all pending claims is maintained under 35 U.S.C. § 101 based upon the allegation that the inventions lack a credible utility. The Examiner argues that homology data is not persuasive because the art recognizes that protein function cannot be predicted based upon homology. The other support discussed in Applicants' previous response is stated to be non-persuasive because figures or tables were not presented and an adequate description of the methods used was allegedly not provided.

In response, Applicants are submitting herewith a Declaration Under 37 C.F.R. § 1.132 executed by Markus Frank, an inventor named on the application. This describes in detail experiments used to support the assertion that the proteins recited in claims act as transporters contributing to drug resistance. However, before considering the Declaration, there are several points that should be mentioned. The first is that the standard of proof needed to fulfill the utility requirement is not one of absolute certainty. Evidence is sufficient if, considered as a whole, it would lead a person of ordinary skill in the art to conclude that an asserted utility is more likely than not true (see MPEP § 2107.02). Thus, the Examiner's arguments with respect to homology data appear to be somewhat misplaced. The relevant issue is not whether this data makes it certain that a protein has the same function as its structural homologue, but whether the homology data, when considered in conjunction with other evidence, makes it more likely than not that they have the same function.

A second point is that a Declaration Under 37 C.F.R. § 1.132, when submitted by an expert in a field, can be used to establish what one of ordinary skill in the art would conclude based upon a given set of experimental results. As long as the statements in the Declaration have a factual basis, as opposed to being purely conclusory, an Examiner must accept the assertions as true or give good reasons for doubting the objective truth of what has been stated (see *Ex parte Copping*, 180 U.S.P.Q. 475, 476 (PTO Bd. App. 1973)).

Finally, it should be recognized that the utility requirement for a claimed composition of matter is fulfilled if an application discloses a single credible use. It is not necessary that *all* uses be explained or that the relationship between all of the activities observed for a protein be understood.

With the above points in mind, the evidence presented by Applicants in the Declaration by Dr. Frank is as follows:

1. Sequence Homology Data: In paragraph 5, section I of the Declaration, Dr. Frank describes the results of a structural comparison made between ABCB5, corresponding to the protein of SEQ ID NO:2 in the application, and two known multidrug resistance proteins, ABCB1 (also referred to as "MDR1") and ABCB4 (also referred to as "MDR3"). It is reported that a 73% homology was observed between the proteins with there being a 54% and 56% amino acid identity, respectively.[1] The way in which comparisons were carried out is described in Appendix II of the Declaration and the results are shown in Figure 1. The Examiner states that sequence homology data is not predictive with respect to function. Although it may be true that homology data cannot, by itself, lead to absolute certainty with regard to function, there is no question that there is a close correlation between structural similarity and functional similarity. Specifically,

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[1] The homology reported in the Declaration, 73%, is actually slightly higher than that reported in the application, 68%. The Examiner indicates that he observed a 57% sequence identity. This appears to correspond approximately to the degree of sequence identity found by Applicants in a comparison between ABCB5 and MDR3. However, homology comparisons may take into account not only sequence identity, but also the substitution of one amino acid for another that has very similar properties. Thus, there is some variation that will depend upon how comparisons are made.

proteins that are highly homologous generally have similar functions. When taken together with the additional factors described below, the homology data presented provides good support for the assertion that ABCB5 should function in a manner very similar to MDR1 and MDR3.

2. Expression Studies: The expression studies described in the Declaration in paragraph 5, section II, demonstrate that ABCB5 is selectively expressed by certain specific cell types, including cancerous cells and cancerous cells that are multidrug resistant. The ABCB5 protein was found to be localized on the cell membrane, as would be expected of a transport protein, and its expression was found to be increased in drug resistant cells (paragraph 5, section II C). Finally, the ABCB5 protein was found to be a marker on progenitor cells. The main importance of this finding with respect to the present discussion, is that this has been a characteristic of other multidrug resistant proteins. Thus, the studies demonstrate a pattern of expression that is consistent with a transport protein involved in conferring drug resistance on cells and which mimics the expression patterns seen with known multidrug resistant proteins. The results are presented in Figures 2-4 and the methodology used is fully described in Appendix II.

3. Transport Studies. In paragraph 5, section III, Dr. Frank describes the results of experiments demonstrating that ABCB5 actively transports rhodamine-123 out of cells. This is one of the main characteristics of multidrug resistance proteins. In addition, experiments were performed demonstrating that incubating ABCB5-expressing melanoma cells with monoclonal antibody against ABCB5 enhances cellular retention of the fluorescent chemotherapeutic drug doxorubucin. This is the result that would be expected if ABCB5 was transporting chemotherapeutic drugs out of cells.

4. Chemoresistance Studies: In paragraph 5 of the Declaration, section IV, Dr. Frank descibes studies examining cisplatin resistance in melanoma cells. Cells that were especially resistant became sensitized to cisplatin when treated with

antibody against ABCB5. This is strong evidence that ABCB5 contributes to drug resistance in cancer cells.

Based upon the results described above, Dr. Frank concludes that ABCB5 most probably functions in transporting drugs out of cells and, earlier in paragraph 5, states his opinion that this evidence would lead others of ordinary skill in the art to draw the same conclusion. Applicants respectfully submit that Dr. Frank is clearly an expert in this field, that the conclusions drawn are based upon experimental results and not merely conclusory and that there is no good basis for doubting the objective truth of the assertions that he makes. It is therefore respectfully requested that the present rejection of claims under 35 U.S.C. § 101 be withdrawn.

B. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

On page 4 of the Office Action, the Examiner rejects claims 39 and 40 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner points out that claim 39 reads in part, "vector comprising a distinct coding element consisting of" and then argues that this is insufficient to make the meets and bounds of the limitation clear.

Applicants respectfully traverse this rejection.

Claim 39 reads:

> 39. A vector comprising a distinct coding element consisting of the nucleotide sequence of the polynucleotide of any one of claims 19-26 or 31-38.

The term "vector" is very commonly used in the art and well understood. Vectors virtually always include sequence elements which constitute restriction enzyme sites. Other elements that are often present include those that promote the replication of the vector after it is transformed into a host cell, a promoter linked to a coding sequence to control expression and, sometimes, other elements that aid in either the transcription of translation of the coding sequence. Present claim 39 includes any vector that has a coding sequence corresponding to the sequence of the polynucleotide of any one of claims 19-26 or 31-38. Thus, the claim includes all expression vectors provided that they include a region with one of the specified sequences.

Applicants do not see any basis for concluding that this claim is indefinite or that it extends beyond the typical vector claims that are found in issued patents. It is therefore respectfully requested that the present rejection be reconsidered and withdrawn.

III. Request for Interview

If the Examiner decides to maintain a rejection of claims under 35 U.S.C. § 101, then Applicants respectfully request an interview to provide Dr. Frank with an opportunity to more fully describe the exact experiments that were conducted and the basis for the conclusions set forth in the Declaration.

Conclusion

In light of the considerations presented above, Applicants submit that all of the Examiner's rejections have now been overcome. It is therefore respectfully requested that these rejections be withdrawn and that the claims presently pending in the application be allowed.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (202) 419-7013.

Respectfully submitted,

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